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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,780	SECOMBES ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55,56,58,60-66 and 68-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55,56,58,60-66 and 68-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/31/05 has been entered.

Applicant's submission of 5/31/05 requested entry of the amendments of 3/29/05, and therefore, those amendments are entered.

Subsequent amendments and arguments of 6/21/05 are entered.

The entry of the above-mentioned amendments places the claims in the following status:

Claims 1-54, 57, 59, and 67 are cancelled.

Claims 55, 58, 60-61, 63-66, and 67, are presently amended.

Claims 68-73 are newly added.

Claim Status, Cancelled Claims

In light of Applicant's cancellation of claims which were rejected and/or objected-to, such objections/rejections are rendered moot, and thus are withdrawn.

Claim Objections

Claims 56 and 69 are objected to because of the following informalities: claims 56 and 69 recite the linking of three items through a single linker. While it is clear that applicant only

claims to link the heavy and light chains with such linker, the claim may also be read to link the secretion signal along with the heavy and light chains with such linker. Appropriate correction is required.

Claim Rejections - 35 USC § 112 – second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 55 is rejected for the limitation "administering to an animal". Specifically, the claims requires such administration to any animal, while the antibody is then expressed in a fish. Moreover, Applicant's argument of 6/21/05 further indicates that they intend to claim administration to a fish (p. 10, last paragraph). Hence, it is clear that Applicant's claim does not reflect what they intend to claim. Amending the claim to recite "administering to a fish" would be remedial.

Claims 55 and 68 each recite "a recombinant antibody molecule derived from an antibody raised against the disease-causing virus...". It is unclear what encompassed by "derived". For example, would antibodies raised against the original antibody be encompassed?

Claims 63 and 73 each recite a monoclonal antibody derived from 3F1H10 "with two amino acid substitutions...." It is unclear whether the derived monoclonal antibody or the 3F1H10 molecule contains such substitutions.

Claims 63 and 73 also recite "and comprises a secretion signal of rainbow trout ... (TGF-[beta])". It is unclear whether the plasmid comprises such signal, or the antibody. Further, if the plasmid comprises such signal, it is unclear how a plasmid could comprise a protein. It is suggested that amending the claims to recite "...and further encodes an operably linked secretion signal of rainbow trout transforming growth factor (TGF-beta)."

Claim 68 recites the limitation "fish". There is insufficient antecedent basis for this limitation in the claim. Further, such lack of antecedent basis makes the claim unclear as to whether it embraces treatment of all fish after the administration to a single fish.

Claims 56-66 and 69-73 are rejected for depending from rejected base claims and not overcoming the lack of clarity in such base claims.

Claim Rejections - 35 USC § 112, first paragraph – enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 55-56, 58, 60-66 and 68-73 remain, or are newly, rejected under 35 U.S.C. 112, first paragraph, for reasons record, because the specification, while being enabling for a composition for protection of a fish against viral haemorrhagic septicaemia virus (VHSV) comprising a non-infectious DNA nucleic acid construct encoding the single chain antibody 3F1H10 that recognizes VHSV, the DNA sequence for the antibody listed on pages 9-10 of the specification and which comprises substitutions of asparagines 35a with threonine and lysine 64 with threonine and is linked at the 5' end to the secretion signal of transforming growth factor

beta, and which sequences is operably linked to the CMV promoter and a polyA tail for protecting a fish against VHSV infection, and vaccines comprising such compositions, and methods of providing prophylactic treatment of fish against VHSV by the administration of these compositions, by injection into the epaxial muscles below the dorsal fin, which compositions transform cells of the muscle tissue local to the injection site and produce secreted 3F1H10 antibodies, thereby producing protection against VHSV, as well as the plasmid vector construct itself, does not reasonably provide enablement for a plasmid encoding any antibody, any secretion sequence, any promoter sequence, any form of administration, any form of composition, treatment of any animal, or any form of treatment for any disease-causing agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The modified rejection now has removed the basis of rejection based on vector type, and on any animal, due to Applicant's amendments.

For the sake of clarity, the rejection repeated below, with particular attention to the present state of the claims. This is followed by a response to Applicant's arguments.

The Law

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its full-claimed scope, and that, therefore, Applicant's claims are not enabled to their full-claimed scope.

It is further noted that this a weighting of factors, and not an 8-prong test. Therefore, any single factor, or even an unlisted factor, may overcome all the factors listed to provide for non-enablement.

The Breadth of the Claims

Claims 55-56, 58, 60-66, and 68-73 are broad in scope. The following paragraphs will outline the full breadth of these claims.

Claims 55-56, 58, and 60-66 encompass methods of passive immunization of a fish against any disease causing virus, comprising the administration, by any method, to any animal, of any plasmid construct comprising a DNA encoding any recombinant antibody derived from any antibody raised against the disease-causing virus, which causes the antibody to be expressed

and secreted cells of the fish upon administration to a fish. Dependent claims limit the antibody molecule to comprise a secretion signal, V-H and V-L domains of an immunoglobulin, all linked together by a single linker sequence; immunodeficient fish; several antibodies to be expressed from the plasmid; a library of antibodies to be expressed from the plasmid; the antibody to be virus-neutralizing; a specific antibody (3F1H10), various administration forms; various administration types; and the administration to multiple plasmids encoding antibodies to a spectrum of viruses' epitopes.

Claims 68-73 encompass similar limitations to 55-56, 58, and 60-66, but simply are drawn to the plasmids as compositions.

Moreover, regarding the compositions, Applicant's only disclosed use for such plasmids is for gene therapy with such plasmids (e.g., SPECIFICATION, e.g., p. 2, paragraph 2; p. 3, paragraph 1; p. 6, paragraph 3). Hence, the compositions would necessarily require the same limitations as the compositions used in the methods.

Because these claims are broad, encompassing compositions and the use of such compositions for treating fish for any disease-causing virus by the administration of a wide range of nucleic acids encoding any antibody or antibodies, without limitation to forms of administration or regulatory constructs, or requiring secretion signal sequences, or requiring that such secretion signal sequences be physically linked to the antibodies, or requiring the linking of three polypeptides by a single fourth polypeptide, the detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide area of knowledge, to a reasonably comprehensive extent. In other words, each of those aspects considered broad must be fleshed out to a reasonable extent so that one of ordinary skill in the art at the time of invention by

Applicant (hereinafter the "Artisan"), would be able to practice the invention, and do so to the fully-claimed scope of invention, without an undue burden being imposed on such Artisan (undue burden). However, as will be discussed below, this burden has not been met.

The Nature of the Invention

The invention is in the nature of compositions for, and methods of performing, gene therapy to treat animals against disease-causing agents.

With regard to gene therapy, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. For example, Deonarain (1998) Expert Opin. Ther. Pat., 8: 53-69, indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequeate levels for a long enough period of time" (p. 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (p. 65, CONCLUSION). Verma (1997) Nature, 389: 239-242, reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (p. 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression ... The use of viruses (viral vectors) is a powerful technique, because many

of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3).

Further, Eck et al. (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, NY., pp. 77-101, states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced, are all important factors for a successful gene therapy (e.g., bridging pp. 81-82). In addition, Gorecki (2001) Expert Opin. Emerging Drugs 6(2): 187-98) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g., ABSTRACT).

Moreover, because Applicant claims so many forms of nucleic acid, each of these forms must be shown to integrate successfully and produce recombinant antibody *in vivo*. One of skill in the art would recognize that each form, single stranded and double stranded and DNA and RNA would have their own mechanisms of incorporation, and such would need to be reasonably predictive to produce transformation of the cells in high enough numbers and produce the protein

in large enough amounts for a long enough period of time to produce a therapeutic effect, which effect may be different if the treatment is prophylactic or after being exposed to any disease causing agent. Treatment would be different because once exposed, the agent has already begun effecting the animal, and therefore not only inhibition of further effects must be accomplished, but removing previously-begun effects must be accomplished.

Furthermore, if the antibody does not have a secretion signal, as embraced by the broad claims, the antibody would not be secreted in the first place, and therefore would exhibit no efficacious treatment. Also, if the secretion signal sequence is not physically linked to the antibody encoding sequence, the antibody would similarly not be secreted.

In reviewing the above-discussed problems, it is clear that the Artisan would therefore require, to make and/or use a new invention in the field, a showing that enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such expression occurs for a long enough period of time to effect treatment. Moreover, without a linked secretion signal sequence, the antibody would not be secreted and have an effect in treatment. Alternatively, direct examples of specific vectors, whether transformed *in vivo* or *ex vivo*, encoding specific antibodies, under the control of specific promoters and other control elements, would overcome this showing for that specific method of administration to that specific species, because, if treatment is successful, it must have met these aforementioned requirements.

The State of the Prior Art

As Applicant states in the specification (p. 18, lines 14-17), there is no art of record demonstrating the establishment of protective immunity to any infectious pathogen in higher vertebrates by administration of genes encoding pathogen-specific sing chain antibodies. However, there exists some art the administration of antibody or antibody-fragment encoding genes as therapy for infectious diseases. Such genes are generally referred to as "intrabodies", as reviewed with respect to antiviral agents (one pathogen type), by Marasco (2001) Curr. Topics Microbiol. Immunol., 260 : 247-70. However, Marasco does not enable, but in fact raises concerns that the Artisan would have with regard to Applicants invention.

Specifically, Marasco is directed to recombinant antibody genes that are expressed intracellularly, and hence do not enable those applications of such genes that are secreted after expression (p. 247, first paragraph). Moreover, with regard to these genes, no *in vivo* studies have been reported, and CTL responses against transduced cells is likely to prohibit their use (p. 253, first full paragraph; p. 264, first full paragraph). Also, one of skill in the art would recognize that multiple genes encoding multiple recombinant antibodies would amplify all of these problems mentioned in the nature of the invention and here. Therefore, one of skill in the art would not only have those issues mentioned in the nature of the invention (above) to consider, but would also need to be able to reasonably predict that CTL responses would not diminish the protective immunity conferred by the administration of the compositions of Applicant's claims.

Hence, the prior art is not only as non-enabling of Applicant's invention as the nature of the invention, but more so, because of the possibility of CTL responses removing any protective effect before it can be established. Hence, because the art is lacking in any examples of nucleic

acids encoding any recombinant antibody that is secreted, and due to the problems mentioned above with regard to gene therapy, each of which are amplified by the use of multiple recombinant antibodies, absent a largely enabling disclosure by Applicant, by way of specific direction and guidance and examples, the invention claimed by Applicant is not enabled for its full scope.

The Level of One of Ordinary Skill in the Art at the Time of Invention

The level of one of skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed to its fully-claimed scope without undue experimentation.

The Level of Predictability in the Art

Because the art, as shown above, is not enabling for new genes encoding monoclonal or polyclonal recombinant antibody compositions and any treatment against disease-causing agents with the same, the Artisan could not predict, in the absence of proof to the contrary, that such applications would be efficacious in any therapeutic application.

Hence, absent a strong showing of guidance and direction and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for its fully claimed scope.

The Amount of Direction and Guidance Provided by Applicant

The specification broadly discusses RNA and DNA constructs encoding antibodies or antibody fragments and their use in conferring protection to any animal against pathogens,

allergens, and toxins (p. 1). Further broad discussion is given to passive immunization, *in vitro* production of antibodies, objects of the invention tracking the claims, a broad belief that the antibodies encoded will act as naturally-occuring host antibodies to confer protection, by binding cells that have been infected by viruses or the viruses themselves, and inhibiting the virus and/or giving the host time to mount an immune response (pp. 1-4). More broad discussion is given to expression vectors, the antibody fragments, a long list of non-comprehensive pathogens, use in immunodeficient humans, allergic reactions and antibodies to IgE, signal sequences, identification sequences, methods of administration, epitopes of the antibodies, and therapeutic compositons (pp. 4-8).

However, such broad discussion does not constitute the specific guidance and direction that would allow the Artisan to predict that any specific recombinant antibody, any form of nucleic acid, any disease-causing agent, any regulatory sequences, any secretion signal not physically linked to the antibody, or the absence thereof, or any form of administration could be used for treatment of any specific condition. The Artisan could not reasonably predict, as reviewed in the nature of the invention and state of the prior art, that enough nucleic acid would reach the target tissue, transform the target tissue, produce enough stable and functional mRNA, and proteins therefrom, and the protein would be stable and functional, and processed correctly, to produce enough of an effect, for a long enough period of time to effect any specific treatment, and, moreover, that CTL responses would not nullify any such effects.

Because of the lack of guidance and direction that would assure the Artisan of the efficacy of such treatments, the examples would be required to provide a very strong showing of

effectiveness. Absent this strong showing in the examples, it would have required undue experimentation to make and/or use the invention within its fully claimed scope.

The Existence of Working Examples

Applicant provides one Example, divided into many parts. Each of these parts will be reviewed sequentially as separate example numbers. Example 1 demonstrates the making of a plasmid vector comprising single chain antibodies. Example 2 demonstrates injection of plasmids of example 1 into fish, into the epaxial muscles below the dorsal fin. Example 3 demonstrates an analysis of the expression of single-chain antibodies in the muscle tissue at the site of injection in example 2. Example 4 demonstrates sampling of the blood plasma from the fish injected in example 2. Example 5 demonstrates that tissue-cultures and plasma samples from fish, each transfected with the plasmids in example 2, exhibit virus neutralizing activity against virulent VHSV. Example 6 demonstrates the protocol used to determine immunoprotection of fish injected in example 2. Example 7 demonstrates single chain antibodies could be detected in the samples collected in example 5. Example 8 demonstrates that cell cultures expressing the single-chain antibodies exhibited better suvival than those not expressing the recombinant antibodies. Example 9 demonstrates the plasma collected in example 4 from fish transformed with the plasmid encoding an antibody expressed the antibody. Example 10 demonstrates that fish transfected with the antibody-encoding plasmid exhibited 81% survival, versus 6% for null-plasmid transfected fish, when challenged with virulent VHSV.

Moreover, it is noted that in these examples, the only plasmid encoding any recombinant antibody is a double-stranded DNA plasmid encoded the single-chain antibody 3F1H10, which has 2 mutations, amino acids 35a and 64 are each substituted with threonine, with the rainbow

trout TGF-beta secretion sequence at its 5' end, and driven by the CMV promoter (p. 11, lines 21-30).

As noted above, in the nature of the invention, this is one example of a specific embodiment which, by way of example, must have met all the requirements to effect prophylactic treatment. However, such examples do not enable other embodiments, due to the reasons given above, in the nature of the invention and state of the prior art. To wit, the Artisan could not reasonably predict in view of the disclosure that multiple antibody genes could be used, any agent could be treated, such treatment could be effected after exposure to the agent, such nucleic acids, of any type of promoter could be used, any type of antibody could be used, or any animal could be treated.

The Quantity of Experimentation Needed to Make and/or Use the Invention

Because of the insufficiency of the working examples, insufficient guidance and direction provided by Applicant, the inherent unpredictability in the art, the state of the art, and the nature of the invention, even in the face of an advanced level of skill in the art, the Artisan would have been required to perform a large amount of experimentation to make and/or use the invention within its fully-claimed scope.

Such experimentation would be required to determine which forms of nucleic acid could be used, which agents could be treated, which animals could be treated, which form of administration could be used, which types of treatment could be effected, which secretion sequences to use, whether to use a secretion sequence, whether multiple genes could be used, which promoters would be required, which immune system deficiencies could be treated, if any,

and whether such treatments would produce enough transformed cells that produce enough stable and functional RNA and proteins therefrom, for a long enough period of time to effect treatment.

Conclusion

Because of the large amount of experimentation required to make and/or use the invention within its fully claimed scope, such experimentation is considered undue, and therefore, such claims are not enabled for any animal, any antibody, any promoter, any form of nucleic acid, any form of composition, any form of treatment, any form of administration, multiple antibody encoding genes, any secretion sequence, the absence of a secretion sequence, or non-operatively linked secretion sequences.

Response to Argument – Enablement

Applicant's argument of 6/21/05 has been fully considered but is not found persuasive.

Applicant argues that the evidence provided in the specification by way of example, and further that the declaration of Dr. Lorensen of 9/16/04, asserting similar results in mice against an unknown toxin (Delcaration of Dr. Lorensen of 6/16/04, paragraph 2), that such data, along with some asserted success in sheep, highly supports the assumption that it is widely applicable throughout the animal kingdom (Applicant's argument of 6/21/05, pp. 9-10).

Such is not persuasive. A smattering of three examples, given the breadth of the number of viruses to which protection is sought, through a wide breadth of antibody types, and given that these examples are in separate species and the methods and constructs used are not given for any except that method in the specification given by way of example, certainly does not overcome the enablement given. It is only proof of specific embodiments, as has been repeatedly stated in the enablement rejection.

Hence, the rejection remains, albeit in modified form due to applicant's amendments.

Claim Rejections - 35 USC § 102 – old rejections, Chang

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 15, 21, and 34 remain rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,543,144 to Chang, filed 21 January 1993; date of patent 6 August 1996.

It is noted that Applicant has incorporated the limitations of the cancelled claims (a secretion sequence) into independent claims 1 and 21, and limited the intended use of the compositions to encoding the antibodies after administration to an animal.

Response to Arguments - 35 USC § 102 – old rejections, Chang

Applicant's arguments of 6/21/05 have been fully considered but are not persuasive.

Applicant argues that Chang teaches administering the nucleic acids to cells, from which the antibodies are collected and administered to patients, and hence the limitations of the claims are not taught. Applicant also asserts that the limitation that the antibody is not encoded until after administration to an animal is also not taught by Chang. (Applicant's arguments of 16 September 2004, pp. 21-22).

Such is not persuasive. Intended use is not considered limiting in art rejections for composition claims: the composition is the composition (MPEP 2111.02 [R-2]). Moreover,

because of the indefinite nature of Applicant's claim (See pages 3-4 of this Official Action), the rejection is maintained, as it meets all the other aspects of the claims.

Finally, Applicant has not overcome the various other aspects of the claims, e.g., in any instance, enough protein being produced and secreted for a long enough period to effect protective immunity or the aspects of CTL responses negating any specific antibody response due to destruction of those cells secreting the antibody.

Hence, Applicant's claims remain non-enabled for the scope given above.

Claim Rejections - 35 USC § 103 – Duan

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 55-56, 58, 60-62, 64-66, and 68-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO Doc. No.: WO 96/37234 to Duan, et al., Filed 23 May 1996, Published 28 November 1996.

With regard to claims 55 and 64, Duan teaches gene therapy by administering a gene that encodes an antibody that binds an antigen associated with a disease (disease causing agent) (ABSTRACT; p. 22, lines 22-29), which may be a virus (e.g., p. 10, paragraph 4), and may be effected by a plasmid encoding the antibody, as such is the standard for electroporation and calcium phosphate co-precipitation (EXAMPLE 4; p. 16, paragraphs 4-5), and hence, the

plasmids would also have to be eukaryotic. One such animal that could be so treated is fish (p. 10, paragraph 3).

However, Duan does not teach the use of secretion sequences, stating:

> Because intracellular expression is desired, the recombinant genes of the invention preferably are prepared so as to be free of a signal sequence. "Free of a signal sequence" means a deletion, mutation or modification of the signal sequence which ordinarily directs antibodies to the secretory compartments. For example, the hydrophobic amino acid core of the signal sequence for secretion can be substituted with hydrophilic residues by site directed mutagenesis. See Biocca, S. et al., "Expression and Targeting of Intracellular Antibodies in Mammalian cells," European Molecular Biology Organization (EMBO) Journal 1: 101 (1990).

(Id., p. 14, paragraph 2)

Moreover, Duan recognizes that passive immunization may be carried out by the use of secretion signal to secrete the antibody, stating:

> Another approach is passive immunization, which involves supplying systemically to a host antibodies that can bind the pathogen. The utility of this approach was greatly increased with the development of humanized antibodies and single-chain antibodies, both of which do not provoke an immune response by the host.
> The forgoing treatments are limited in that the most active site for many diseases is within the cell, beyond the reach of antibodies. In addition, synthetic antibodies have a relatively short half-life, during which they are subject to serious proteolytic and other degradation.

(Id., p. 2, paragraphs 4-5).

Hence, Duan is recognizing that including the secretion signal will allow extracellular secretion and protection, which, although it may be limited, is evidenced by Duan to be efficacious. Also, because Duan teaches the method, Duan is teaching the compositions.

Therefore, at the time of invention by Applicant, it would have been obvious to modify the method of Duan to treat fish with plasmid encoding a generic antibody against

a virus, and including a secretion signal. The Artisan would have been motivated to do so in order to treat virus infections extra-cellularly. Moreover, the Artisan would have had a reasonable expectation of success, as Duan had already demonstrated that the intracellular antibodies would work, and recognized the use of passive immunity in the art.

With regard to claims 56 and 69, Duan teaches the V-H and V-L chains, linked by a linker (p. 14, paragraph 4).

With regard to claim 58, Duan teaches treating animals where regular vaccines are incapable of treating an individual, and as such, the animals must be immunodeficient for reacting to that specific pathogen.

With regard to Claims 60 and 70, Duan teaches that multiple antibodies to distinct epitopes may be used (p. 22, line 30-p. 23, line 9).

With regard to claims 61 and 71, the teaching of Duan that multiple antibodies to distinct epitopes may be used (ABOVE), is a teaching of a gene expression library of antibodies to the disease-causing virus.

With regard to claims 62 and 72, Duan teaches virus-neutralizing antibodies (EXAMPLE 23).

With regard to claim 64, Duan teaches intravenous, perfusion, and topical treatment (p. 17, lines 15-18) which encompasses at least liquids, ointment, and paint.

With regard to claim 65, Duan teaches intravenous, perfusion, and topical treatment (p. 17, lines 15-18), which encompasses at least injection.

With regard to claim 73, Duan teaches the use of more than one vector (p. 16, paragraph 4).

Response to Argument – Anticipation, Duan

Applicant's arguments of 6/21/05 have been fully considered but are not found persuasive.

Applicant argues that Duan's reference to a secretion signal may be something in the prior art, but only for tissue culture experiments, and as such it is not an improvement over the prior art (Applicant's argument of 6/21/05, p. 11, paragraph 2).

Such is not persuasive. Duan's experiments are not at issue, and Applicant has failed to provide any evidence that there exists no reasonable expectation of success for modifying Duan's methods to express a secreted antibody. Applicant's arguments are simply conclusory.

Hence, the rejections are maintained on the newly-presented claims.

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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